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Patent Application

## FIBER-OPTIC FLOW CELL AND METHOD RELATING THERETO

## CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of U.S. Provisional Patent Application  
5 serial number 60/422,495, entitled "Device for Liquid and Air Sampling and  
Detection Using Optical Fiber-Based Sensors," filed October 31, 2002, which is  
incorporated by reference herein in its entirety.

## FIELD OF THE INVENTION

10 The present invention relates to flow cells. In particular, it relates to a flow  
cell having a grating-based optical fiber sensor incorporated therein.

## BACKGROUND OF THE INVENTION

Flow cells have been constructed for liquid-phase measurements using  
15 fluorescent-based devices that require the sensor surface to be in contact with the  
environment. These flow cells are primarily designed to enhance the sensing  
characteristics of a particular component by blocking background light from  
influencing the sensor response. The device enclosure is constructed in a way to limit  
background light, a primary noise factor in fluorescent applications. Because the  
20 primary purpose of the cell is to control coupled light, the cell does not take into  
account rigid support for the optical fiber or additional processing needs such as mode  
stripping. In addition, flow cells have configurations that require external pumps or  
other methods to bring the external environment to the sensor as opposed to directly  
exposing the sensor to the external environment.

25 Crotts et al. (U.S. Patent No. 6,215,943 B1) describe an optical fiber holder  
that allows a sample to be tested while avoiding strain and bending influences. The  
holder comprises a tube having a longitudinal axis, a first end for receiving an optical  
fiber and a recessed second end for protecting the optical fiber tip. An aperture is  
disposed along a length of the longitudinal axis of the tube for exposing the optical  
30 fiber to a sample. A change in a sample is determined by disposing an optical fiber  
device having a sensing element into the optical fiber holder. The optical fiber holder  
is then inserted into a vessel containing a sample and the sample is circulated past the

sensing element. The problem with this device is that it requires that a large enough sample volume be available to submerge the device and to circulate the sample past the sensor. Therefore, small (microliter) samples cannot be used. In addition, there is no way to control the manner by which the sample contacts the sensor. This is of  
5 particular importance when one desires to conduct kinetic studies. Kinetic studies and studies where it is desirable to obtain results in real-time as various samples come into contact with one another are difficult to conduct with this device because the method of dipping is limited by diffusion. Moreover, this configuration is only applicable to large sample sizes. When sample sizes are on the microliter scale, the holder is  
10 reduced dimensionally and loses its structural rigidity and, hence, its capability to measure adequately.

Malmqvist et al. (U.S. Patent No. 6,200,814 B1) provides a method and device for controlling a fluid flow over a sensing surface within a flow cell. The methods employ laminar flow techniques to position a fluid flow over one or more discrete  
15 sensing areas on the sensing surface of the flow cell. Such methods permit selective sensitization of the discrete sensing areas, and provide selective contact of the discrete sensing areas with a sample fluid flow. The method requires that the surface of the sensor be sensitized by activating the sensing surface such that it is capable of specifically interacting with a desired analyte. The sensor device comprises a flow cell having an inlet end and an outlet end; at least one sensing surface on a wall surface within the flow cell located between the inlet and outlet ends; wherein the flow cell has at least two inlet openings at the inlet end, and at least one outlet  
20 opening at the outlet end, such that separate laminar fluid flows entering the flow cell through the respective inlet openings can flow side by side through the flow cell and contact the sensing surface. In this aspect, the flow cell and the sensing surface are one in the same. In another aspect of the invention, the sensor system comprises a flow cell having an inlet end and an outlet end; at least one sensing area on a sensing surface within the flow cell between the inlet and outlet ends; the flow cell having at  
25 least two inlet openings at the inlet end, and at least one outlet opening at the outlet end; means for applying laminar fluid flows through the inlet opening such that the laminar fluid flows pass side by side through the flow cell over the sensing surface; means for varying the relative flow rates of the laminar flows of fluids to vary the  
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respective lateral extensions of the laminar flows over the sensing surface containing the sensing area or areas; and, detection means for detecting interaction events at the sensing area or areas. These flow cells are designed such that the sensing surface is a part of the wall surface within the flow cell. When the sensor is part of the flow cell wall, there is no way to route an optical fiber. Thus, the flow cell design does not allow incorporation of an optical fiber sensor.

Jorgenson et al. (U.S. Patent Nos. 5,359,681; 5,647,030; and 5,835,645) disclose a fiber optic sensor which detects a sample in contact with the sensor by surface plasmon resonance (SPR) measurements. The sensor includes a surface plasmon supporting metal layer in contact with an exposed portion of the optical fiber core. Detection of a sample with the fiber optic SPR sensor is made, in part, by contacting the sample with the sensing area of the optical fiber. The sensing area is made by exposing a portion of the optical fiber core by removal of the surrounding cladding or cladding(buffer layers, and adhering an SPR supporting metal layer to the exposed optical fiber core. The SPR supporting metal layer of the optical fiber is then exposed to the sample of interest, and the refractive index of the sample is determined. The problem with this configuration is that it is difficult to keep the optical fiber straight while mass producing the flow cell with consistency. Moreover, the invention does not address a method for optimizing sampling.

An object of the present invention is to provide a flow cell that allows for various studies to be conducted on a sample or a variety of samples and sample combinations.

Another object of the invention is to provide a flow cell that employs a grating-based optical fiber sensor system.

Another object of the invention is to provide a flow cell that is capable of operation under varying flow rates with varying sample sizes.

Another object is to present a flow cell that permits measurement of reaction rates.

Another object of the invention is to provide a flow cell that is easy to manufacture and assemble with consistency.

Another object of the invention is to provide a flow cell that can be easily modified to achieve the desired testing apparatus.

Another object of the invention is to provide a flow cell design that provides the flexibility to increase the number of sample channels without comprising the ability of the sensors within the flow cell to make accurate measurements.

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### SUMMARY OF THE INVENTION

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By the present invention, a flow cell is presented. The flow cell comprises a substrate having at least one sample channel and at least one optical fiber channel holder. At least one optical fiber is disposed within each optical fiber channel holder. Each optical fiber has at least one grating. Each optical fiber grating is in contact with each sample channel, defining a sensing area. At least one sample port is positioned in an operable relationship to at least one sample channel.

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In a further embodiment of the invention, the flow cell has at least one sample outlet positioned in an operable relationship to at least one sample channel. The flow cell may be of a monolithic or piece-like structure. A flow cell kit contains at least two mating pieces that may be reconfigured in a number of arrangements depending on the desired application. The flow cell is used for conducting measurement studies on a neat sample or a complex mixture on a range of sample sizes, including samples of less than 100 microliters.

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An advantage to these arrangements is that the optical fiber channel has sections in the flow cell where the optical fiber is isolated from the sample channel. This permits easy manufacturing of the flow cell without disturbing the configuration of the sample channel.

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Additional objects and advantages of the invention will be set forth in part in the description which follows, and in part will be obvious from the description, or may be learned by practice of the invention. The objects and advantages of the invention will be obtained by means of instrumentalities in combinations particularly pointed out in the appended claims.

### BRIEF DESCRIPTION OF THE DRAWINGS

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The accompanying drawings illustrate a complete embodiment of the invention according to the best modes so far devised for the practical application of the principles thereof, and in which:

FIG. 1 is a cross sectional view of a flow cell embodiment having two sample ports that act as either an inlet and/or an outlet; a single sample channel; and a single optical fiber channel holder.

FIG. 2A is a cross-sectional view of the flow cell having two mating pieces.

5 FIG. 2B is a cross-sectional view of the flow cell assembly when the two mating pieces are assembled together.

FIG. 3 is a cross-sectional view of the flow cell having three mating pieces.

FIG. 4 is a cross-sectional view of the flow cell having a single sample port and a plurality of sample channels.

10 FIG. 5 is a cross-sectional view of the flow cell having a plurality of sample ports, a single sample channel, and a single sample outlet.

FIG. 6 is a cross-sectional view of the flow cell having one sample port, a plurality of sample channels, and one sample outlet.

15 FIG. 7 is a cross-sectional view of the flow cell having one sample port, a plurality of sample channels, and a plurality of sample outlets.

FIG. 8 is a cross-sectional view of the flow cell having a plurality of sample ports, one sample channel, and one sample outlet.

FIG. 9 is a cross-sectional view of the flow cell having a plurality of sample ports, one sample channel, and a plurality of sample outlets.

20 FIG. 10 is a cross-sectional view of the flow cell having a plurality of sample ports, a plurality of sample channels, and a plurality of sample outlets.

FIG. 11A is a perspective view showing a flow cell array formed by stacking several flow cells together.

FIG. 11B is a 3-dimensional view showing a stacked flow cell array.

25 FIG. 12 is a schematic showing a flow cell array integrated with other processes.

FIG. 13 is a graph depicting the reaction kinetic data when the flow cell of the present invention is in use.

### 30 DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

Referring now to the drawings, where similar parts are numbered the same, Figure 1 depicts a simple embodiment of the invention where the flow cell **10**

comprises a substrate **20** having at least one sample channel **30** and at least one optical fiber channel holder **35** disposed therein. For the purpose of this application and the appended claims, an optical fiber channel holder is a holder that is capable of achieving precision alignment and consistent tension on the optical fiber. At least one optical fiber **40** is disposed within each optical fiber channel holder **35**. The optical fiber **40** has at least one grating **50** disposed therein. The optical fiber channel holder **35** is designed to come into contact with the sample channel **30** at the points along the optical fiber where each optical fiber grating **50** is located. These points define a sensing area **55**. At least one sample port **60** is positioned in an operable relationship to at least one sample channel **30** to permit introduction of a sample into the sample channel. Although two sample ports are depicted, it is understood that there need only be one sample port. When the flow cell has one sample port, the sample is introduced into and exits from the flow cell through the same port. The sample port **60** is positioned in an operable relationship to the sample channel **30** such that the sample may easily flow into the sample channel. In one embodiment of the invention, where the flow cell comprises more than one sample port, at least one sample port is plugged with a gas permeable material that allows air to escape as a sample is introduced into another sample port. Alternatively, a pump is attached to at least one sample port to serve as a means for either drawing or pushing the sample through the flow cell. Lastly, the sample port may serve as an exit port for the sample after it flows through the flow cell. Multiple sample ports may be employed when the user desires to introduce multiple samples into the flow cell. Alternatively, a pipette tip is formed on the sample port for drawing fluid samples into the sample channel and through the substrate. This is especially desirable when a microtiter plate arrangement is employed.

The sample channel is capable of being modified to achieve the desired sample delivery volume to the sensing area (preferably less than 100 microliters). The sample channel **30** is depicted in its preferred configuration where the sample channel is curved to provide optimal fluid flow within the sensor area. The curved shape allows the flow to be laminar, thus eliminating dead volumes. However, various geometries may be employed to enhance downstream and upstream flow of the sample. Alternatively, the sample channel **30** may also be straight to easily

prevent samples from being trapped in the flow cell provided it is in contact with the grating portion of the optical fiber.

The optical fiber 40 is positioned within an optical fiber channel holder 35.

Each optical fiber has a grating 50. The portion of the optical fiber having the grating 50 is positioned within the optical fiber channel holder 35 so that the grating 50 is in contact with the sample channel 30, defining a sensing area 55. This is the area where the sample contacts the optical fiber. The amount of sample flowing into the sensing area is controlled by modifying the dimensions of the sample channel by using different geometries. The optical fiber has, at a minimum, one grating disposed therein. The grating is either a Bragg grating or a long period grating, depending on the sample under test. More than one grating is disposed within the optical fiber when multiple test points are desired. When multiple gratings are disposed within the optical fiber, the optical fiber channel holder is configured such that each grating contacts the sample channel. Moreover, the optical fiber may be pre-treated with a reactive coating prior to insertion into the optical fiber channel holder. Reactive coatings are those coatings that are capable of undergoing a change when exposed to a specific parameter such that it causes the long period grating to produce a wavelength transmission spectrum functionally dependent on the change which takes place.

These types of coatings are described in U.S. Patent No. 5,864,641 to Murphy et al. which is hereby incorporated by reference in its entirety. Alternatively, the optical fiber may be treated in-situ by flowing a sample containing a reactive species over the optical fiber grating prior to introducing the sample into the flow cell. The optical fiber is connected to an optical light source and a detector using procedures known to those of skill in the art.

The design of the flow cell of the present invention overcomes the problem of Crotts et al. where large sample sizes are required. The novelty of the invention lies in the optical fiber channel holder 35 which helps the optical fiber sustain a linear shape and avoid possible distortion when it comes into contact with a sample. This aids in preventing optical distortions that result when the optical fiber is subject to sudden movements experienced when various samples come into contact with the optical fiber. This design is preferred over a design where the optical fiber is disposed within the sample channel because the optical distortions are reduced if not

eliminated. Moreover, the optical fiber channel holder enables the optical fiber to be routed through the flow cell and facilitates alignment and simplifies fabrication procedures such that the configuration of the sample channel is not disturbed.

The substrate **20** gives rise to the overall shape of the flow cell **10** and is either a monolithic structure or a piece-like structure. In the case of a monolithic structure, the substrate is pre-cast or a solid piece that has been bored-out to provide at least one sample channel **30**, at least one optical fiber channel holder **35**, and at least one sample port **60**. The flow cell **10** is any shape suitable for the desired application. In particular, the flow cell is either a cylinder or a planar (meaning 2-dimensional) structure.

Figures 2A and 2B depict a flow cell **10** comprised of two mating pieces **70**, **80**. The upper portion **70** of the mating pieces contains at least one sample channel **30** and at least one sample port **60**. Figure 2A and 2B show a preferred embodiment where there is a sample outlet **75** in fluid connection with the sample channel **30** such that the sample is removed from the flow cell through the sample outlet **75**. The lower portion **80** of the mating pieces comprises at least one optical fiber channel holder **35** having an optical fiber **40** with a grating **50** disposed therein, positioned within the optical fiber channel holder **35**. The optical fiber channel holder **35** is, in this instance, drilled out of the base such that it is essentially parallel to the sensing area. The figures also depict an embodiment where an optical fiber connector **45** is disposed within the flow cell and forms an input/output connection with the optical fiber. Figure 2B shows a further embodiment of the invention where an injection port **32** has been incorporated with the sample port for introduction of a sample by injection. Thus, the flow cell has both an optical and a fluid connection within it.

Figure 2B depicts the structure of the flow cell when the mating pieces have been assembled together. The resulting structure may be of any geometric shape known to those of skill in the art. Preferably, the mating pieces give rise to a cylinder or planar structure. When the need arises, one may incorporate various sealing means, such as gaskets, to prevent leakage. Figure 2B shows a sealing means **33** disposed at various junctures in the flow cell to prevent fluid leakage. Such sealing means may be of any means known to those of skill in the art such as gaskets, adhesives, and various sealing compounds.

Figure 3 depicts an alternative embodiment of the flow cell 10 comprised of three mating pieces. In this embodiment, there is an upper section 100 containing at least one sample channel (not shown) and at least one sample port 60. This portion is counter-sunk to permit critical alignment of the optical fiber channel holder 35 with the sample channel 30. In the middle section 110, there is the optical fiber channel holder 35 having the optical fiber 40 disposed therein. The optical fiber channel holder 35 is configured to allow a space defining a sensing area 115 where the grating portion of the optical fiber 40 is located. The optical fiber channel holder is designed such that the sensing area and flow cell walls are close to the fiber for diffusion purposes. The lower section 120 of the flow cell serves as a support or base for the assembly. As with the upper portion, the lower section 120 is also counter-sunk to permit critical alignment of the optical fiber channel holder 35 with the sample channel 30. The flow cell assembly is joined and held together by a fastener. Any fastener known to those of skill in the art may be used. Examples of such fasteners include but are not limited to: screws; nuts and bolts; male-female connectors that are fabricated as part of the substrate; rivets; welds; adhesives; straps; crimp connectors such as bent wire; bands fabricated from rubber, metal, plastic; and clamps such as C-clamps. The use of multiple mating pieces allows the user to modify the flow cell or reconfigure it. For example, an upper section containing a single sample channel having one sample port may be substituted with an upper section having multiple sample channels having either one or multiple sample ports. If desired, the upper section may also contain a sample outlet or multiple sample outlets so the sample is removed from the flow cell through an outlet other than the sample port.

Alternatively, the middle section may be exchanged to match the number of sample channels of the upper section or may provide a single sensing area where many samples converge. When the need arises, one may incorporate various sealing means, such as gaskets, to prevent leakage. Because of the versatility afforded by having a piece-like structure, a flow cell kit is provided that allows the user to design custom flow cells depending on the application. The kit configuration makes the flow cell easy to clean. The ability to disassemble the flow cell easily allows for the user to apply various coatings to the cell that can be removed without causing damage to the flow cell. A flow cell comprised of mating pieces provides a significant advantage

over the prior art flow cells because it is easy to clean; can be easily converted for a particular application; provides consistent manufacturing and test results; and provides the flexibility to increase the number of sample channels without compromising the measurements made in the sensing area.

5 Figures 4 and 5 show alternative embodiments of the invention where the number of sample ports and sample channels are varied and the sample port serves as both an inlet and an outlet for the sample. In these configurations, the sample channel 30 terminates with a sample reservoir 37. This permits the sample to be contained within the flow cell after it has passed through the sensing area 55. Figure 4 depicts  
10 an embodiment where there is one sample port 60 and a plurality of sample channels 30. In this arrangement, the sample enters and exits the flow cell 10 through the sample port 60. The optical fiber 40 is disposed within the optical fiber channel holder 35. Sample measurements are made in the sensing area 55 where the optical fiber grating 50 is in close proximity to the sample channel 30. Figure 5 shows an  
15 alternative embodiment that allows samples to be mixed within the flow cell 10. In this embodiment, a plurality of sample ports 60 are provided but only one sample channel 30, terminating with a sample reservoir, is provided. The optical fiber 40 is disposed within the optical fiber channel holder 35. A plurality of samples are introduced through the sample ports 60, mixed in the sample channel 30, and detected  
20 in the sensing area 55 of the flow cell where the grating 50 is in close proximity to the sample channel. The mixed sample is removed from the flow cell through the sample ports 60 upon completion of the data collection process. Both figures depict a  
25 preferred embodiment where an optical fiber connector 45 is attached to an end of the optical fiber 40.

Figures 6-9 show further embodiments of the invention, where the number of sample ports, sample channels, and sample outlets are varied. Figure 6 depicts an embodiment of the flow cell 10 having one sample port 60, a plurality of sample channels 30, and one sample outlet 75. In addition, the flow cell 10 has a fastening means 112 such that it may be interlocked with other flow cells. An optical fiber channel holder 35 is positioned in an operable relationship to each sample channel 30 such that, for each sample channel 30, there is an optical fiber channel holder 35 positioned in an operable relationship to it. Each optical fiber channel holder 35 has  
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an optical fiber **40** disposed within it. Preferably, each optical fiber **40** has an optical fiber connector **45** attached to an end of the optical fiber **40**. This configuration permits multiple readings to be taken on a single sample. Figure 7 depicts an embodiment of the invention where there is one sample port **60**, a plurality of sample channels **30**, a plurality of optical fiber channel holders **35** each having an optical fiber **40** disposed therein, and a plurality of sample outlets **75**. Each optical fiber **40** has an optical fiber connector **45** affixed to an end of the optical fiber **40**. This arrangement allows multiple readings on a single sample with quick removal through the sample outlets **75**. Figure 8 shows an embodiment where the flow cell **10** has a plurality of sample ports **60**, one sample channel **30**, one optical fiber channel holder **35** having one optical fiber **40** disposed therein and terminating at one end with an optical fiber connector **45**, and one sample outlet **75**. This configuration allows for sample mixing in the sample channel **30** by allowing different samples to be introduced into the flow cell. Also depicted is a fastening means **112** for assembling the flow cell **10** with other flow cells. The flow cell **10** of Figure 9 has a plurality of sample ports **60**, one sample channel **30**, one optical fiber channel holder **35** having one optical fiber **40** disposed therein and terminating at one end with an optical fiber connector **45**, and a plurality of sample outlets **75**. This configuration allows for mixing of samples in the sample channel **30** plus quick removal of the sample through the sample outlets **75**. In addition, fasteners **112** are provided for assembling the flow cell **10** with other flow cells.

Figure 10 depicts another embodiment of the invention where the flow cell **10** comprises a plurality of sample ports **60**; a plurality of sample channels **30**; a plurality of optical fiber channel holders **35** having one optical fiber **40** disposed therein and terminating at one end with an optical fiber connector **45**, and a plurality of sample outlets **75**. This configuration provides the user with the ability to inject many different samples into the flow cell **10** through the sample ports **60** and removal of the samples through the sample outlets **75**. In addition, fasteners **112** are provided for assembling the flow cell **10** with other flow cells.

Figures 11A and 11B depict how a flow cell array **125** is assembled by stacking various flow cell assemblies **10** together. Each flow cell **10** has a means for interlocking with another flow cell (not shown). In a most preferred embodiment of

the invention, the flow cell has at least one sample outlet 75, at least one sample channel 30, and 2, 8, 96 384, or 1536 sample ports. In addition, each flow cell has at least one sample port 60. Also depicted is a preferred embodiment where each optical fiber (not shown) terminates with an optical fiber connector 45. When there are  
5 multiple sample channels, each channel is spaced apart a distance of less than or about 9mm. This spacing makes the flow cell compatible with micro titer plates which are the sample plates used in life sciences research. The tip volumes and spacing between the tips are designed into the flow cell for microtiter interface. In addition, when the flow cell comprises mating pieces, quadrant sampling can be used to interface with  
10 high capacity plates such as 384 and 1536 micro titer plates (Figures 11A and 11B).

As a further embodiment to the invention, each sample port has a means to control delivery of the sample into each sample channel. Such means may be any known to those of skill in the art. In particular, the means may be by aspiration, continuous flow, and continuous flow with dwell time when there is no sample outlet.  
15 If a sample outlet is part of the flow cell, then the means may also include a continuous loop. When a sample is introduced by aspiration, it undergoes a back and forth motion within the sample channel. Continuous flow involves the movement of the sample into the portion of the sample channel containing the optical fiber in such a way that there is no dynamic recycling of the sample. When there is continuous flow  
20 with at least one dwell time, the sample is stopped and held for a certain length of time at the grating location on the optical fiber. Continuous looping of a sample involves moving the sample within the sample channel in such a way that the sample is exposed to the grating on the optical fiber multiple times in a circular or looping configuration such that the sample coming from the sample output is re-fed at the sample port. Alternatively, a sample undergoing continuous looping can undergo a  
25 certain dwell time within the sensing area before the sample is re-fed at the sample port.

The samples employed in the present invention may be of any type known to those of skill in the art. In particular, the sample is selected from the group consisting of: a liquid sample, a gas sample; and a complex sample. Combinations of these sample types may also be employed. For example, a liquid sample and a gas sample may be injected into two different sample ports and mixed in the sample channel. A  
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complex sample is defined as a sample that is heterogeneous in composition.

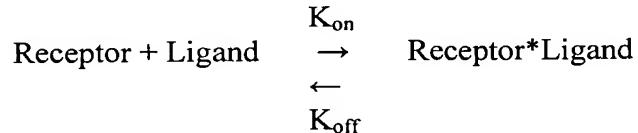
Examples of complex samples include but are not limited to: whole blood; serum; grain mixtures; slurries; milk; urine; saliva; and spinal fluid.

The flow cells of the present invention are used to conduct measurement studies on a sample and the flow cell. When the flow cell has no sample outlet, the sample is introduced into the sample port, allowed to flow into each sample channel, and certain characteristics of the sample and the flow cell are measured at the point or points on the optical fiber where the grating is located. After the measurements are completed, the sample is removed from the sample channel through the sample port.

Alternatively, if the flow cell contains a sample outlet, the sample is removed through the sample outlet. Various physical characteristics of the sample are measured such as temperature, pressure, refractive index, and pH. These characteristics are based on the relationship of the sample to that of the portion of the flow cell where the optical fiber grating is located.

Alternatively, the flow cells of the present invention are used to measure chemical characteristics of a sample. These changes are based on the actual chemical composition of the sample. For example, the biochemical changes taking place in the sample may be measured. In addition, the biological target concentration, pH, reaction rates and chemical target concentrations may be measured in a sample.

For example, the flow cell may also be used for kinetic studies. Kinetic studies are conducted by treating the optical fiber sensor with ligands that react with targets contained in the sample over a certain time period. The interactions provide information about  $K_d$  and  $K_a$  coefficients. The flow cell described herein can be used to establish the kinetic binding values of rate of association ( $K_{on}$ ), rate of dissociation ( $K_{off}$ ), and calculate the equilibrium dissociation constant ( $K_d$ ). The following model is used to illustrate the relationship between the values:



The interaction of the receptor, which is immobilized on the fiber, and the ligand results in a receptor-ligand complex. The rate of this complex formation is the rate of association or  $K_{on}$  rate. The formed complex can also dissociate to the free receptor and ligand which is the rate of dissociation or  $K_{off}$ . When equilibrium is achieved the rate of association is equal to the rate of dissociation and is referred to the equilibrium dissociation constant ( $K_d$ ) and is defined by the ratio  $K_{off}/K_{on}$ . When the concentration of ligand equals the  $K_d$ , half the receptors will be occupied at equilibrium. If the receptors have a high affinity for the ligand, the  $K_d$  will be low, as it will take a low concentration of ligand to bind half the receptors.

Figure 12 depicts how a flow cell array is integrated with other processes. This integration is useful for lab-on-a-chip type applications. In this embodiment, a flow cell array 125 is integrated with other processes on a chip. Multiple fiber optic grating sensors 130 are in contact with at least one sample channel 135 to form the sensing area 140. An optical fiber connector 145 is disposed on one end of the optical fiber grating sensors 130.

## EXAMPLES

### Example 1

A Protein A coated sensor was prepared by providing a glass fiber having a long period grating (LPG) disposed therein. The glass fiber was cleaned with a solution of methanol and hydrochloric acid in a 1:1 mixture for one hour at room temperature. The fiber was rinsed with methanol. The fiber was soaked in a 10% solution of (3-Glycidoxypropyl)trimethoxysilane in methanol for one hour at room temperature. The fiber was then rinsed with methanol. Next, the fiber was soaked in a phosphate buffered saline solution, pH 7.4 containing 100 ug/ml Protein A for one hour. The fiber was rinsed with phosphate buffered saline solution, pH 7.4 and stored in the same buffer at 2-8 degrees C.

Example 2

The Protein A coated sensor of Example 1 was used to monitor the response of the sensor to rabbit IgG. The Protein A coated sensor was exposed to a phosphate buffered saline solution, pH 7.4, (PBS) to establish a baseline signal for the sensor.

5       The sensor was then exposed to varying concentrations of rabbit immunoglobulin (IgG, Technical grade available from Sigma) in PBS pH 7.4. As shown in FIG 13, the rabbit IgG bound to the protein A on the surface on the fiber sensor. The magnitude of the response was dependent upon the concentration of rabbit IgG. To remove any unbound material from the sensor surface, the fiber was exposed to PBS pH 7.4.

10      Next, the fiber was exposed to 10 mM HCl to remove the bound IgG material from the Protein A and to regenerate the fiber for a subsequent assay cycle. Lastly, the fiber was exposed to a PBS pH 7.4 buffer solution to re-establish a baseline and return the sensor to a buffered environment.

15      Testing for this example took place in a single channel flow cell with multiple repetitions. The flow cell configuration consisted of a 3 part flow cell shown in Figure 1. The flow cell overall dimensions were [60 mm length x 26 mm width x 12.6 mm height]. The sample channel was 1 mm outer diameter throughout the flow cell. The long period grating (LPG) sensing element was 1mm long with a 125 micron outer diameter. The substrate holder that housed the optical fiber channel holder had a sampling window that was 1 mm wide x 13 mm long. The substrate holder was 0.5 mm thick. By changing the sensing element surface area and varying the flow cell dimensions, smaller volumes can be achieved during testing.

20      The above description and drawings are only illustrative of preferred embodiments which achieve the objects, features and advantages of the present invention, and it is not intended that the present invention be limited thereto. Any modification of the present invention which comes within the spirit and scope of the following claims is considered part of the present invention.